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EXAMINER	
DOWELL, PAUL THOMAS	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/615,039	MORIN ET AL.	
	Examiner	Art Unit	
	Paul Dowell	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-46* is/are pending in the application.

4a) Of the above claim(s) *39 and 41-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-38 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/11 & 7/11: 2000*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of claims 27-38, 40 (group I) in the reply filed on 1/27/2006 is acknowledged.

Claims 39, 41-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/27/2006.

Applicant's election **with traverse** of SEQ ID NO:1 in the reply filed on 1/27/2006 is acknowledged. Applicants argue that the extensive teachings disclosed in the specification would allow the skilled reader to readily produce a genus of promoter sequences suitable for use in the recombinant virus that is claimed and therefore there should be no restriction to either SEQ ID NO:1 or SEQ ID NO:2. Applicant's arguments have been fully considered but they are not persuasive. Examiner maintains that SEQ ID NO:1 is structurally distinct from SEQ ID NO:2 as put forth in the restriction requirement of 1/11/2006 and that the search required for SEQ ID NO:1 ***and*** SEQ ID NO:2 is not co-extensive and as such represents an undue burden. Therefore, the restriction requirement of 1/11/2006 is made **FINAL**.

Examiner acknowledges Applicant's statement in the reply filed on 1/27/2006:

> In the event that the restriction between SEQ ID NOs:1 and 2 is made final, applicant requests that SEQ ID NO:2 and its variants be rejoined into the application upon determination that the claimed invention is free of the prior art.

Claims 27-38 and 40 are under examination in the instant office action.

Information Disclosure Statement

The information disclosure statements of 7/11/2000 and 10/11/2000 have been considered. However, reference G of the 7/11/2000 IDS and references C, F and H of the 10/11/2000 IDS are not written in the English language. Further, references NNN and OOO of the 7/11/2000 IDS do not have publication dates. For these reasons, these specific references have not been considered and a line has been drawn through said references on the PTO-1449 forms included in the instant office action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-38, 40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 12-16 of U.S. Patent No. 6,777,203. Although the conflicting claims are not identical, they are not patentably distinct from each other because each are drawn generally to a recombinant virus having a genome comprising specific regions of the hTERT promoter operably linked to a heterologous encoding nucleic acid. It is noted that claim 15 of '203 recites "a viral vector comprising the polynucleotide of claim 1".

Claims 27-38, 40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 11, 14-23, 26-34 of U.S. Patent No. 6,610,839. Although the conflicting claims are not identical, they are not patentably distinct from each other because each are drawn generally to a recombinant virus having a genome comprising specific regions of the hTERT promoter operably linked to a heterologous encoding nucleic acid. It is noted that claims 8 and 21 of '839 recite "the nucleic acid of claim 2, contained in a viral vector" and "the nucleic acid of claim 17 contained in a viral vector", respectively.

Claim Objections

Claim 37 is objected to as being drawn to a non-elected invention. Specifically, claim 37 recites promoter polynucleotides comprising either SEQ ID NO:1 or SEQ ID

NO:2. In the response of 1/27/2006, Applicants elected SEQ ID NO:1. It is noted that for the purposes of examination, ***Examiner has interpreted claim 37 to read only on SEQ ID NO:1*** and not SEQ ID NO:2 because of Applicant's election of SEQ ID NO:1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 27, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A recombinant virus having a genome in which a promoter polynucleotide is operably linked to a genetic element essential for replication or assembly of the virus, wherein the promoter polynucleotide consists of no more than 82 consecutive nucleotides consisting of the sequence from position –117 to position –36 relative to the translation initiation site (position 13545) of SEQ ID NO:1, and wherein the promoter polynucleotide preferentially promotes transcription of the genetic element in cells expressing telomerase reverse transcriptase (TERT), thereby promoting replication of the virus, and wherein replication of the virus in a cell leads to lysis of the cell; and a method for producing said recombinant virus,

does not reasonably provide enablement for:

A recombinant virus having a genome in which a promoter polynucleotide is operably linked to a genetic element essential for replication or assembly of the virus, wherein the promoter polynucleotide consists of any consecutive 82 nucleotides of SEQ ID NO:1, and wherein the promoter polynucleotide preferentially promotes transcription of the genetic element in cells expressing telomerase reverse transcriptase (TERT), thereby promoting replication of the virus, and wherein replication of the virus in a cell leads to lysis of the cell; and a method for producing said recombinant virus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claim 27 is drawn to a recombinant virus having a genome in which a promoter polynucleotide is operably linked to a genetic element essential for replication or assembly of the virus, wherein the promoter polynucleotide preferentially promotes transcription of the genetic element in cells expressing TERT, thereby promoting replication of the virus, and wherein replication of the virus in a cell leads to lysis of the cell. The breadth of claim 27 is such that it reads on any promoter polynucleotide, wherein the promoter polynucleotide preferentially promotes transcription of said genetic element in cells expressing TERT. Claim 38 further limits claim 27 to wherein the promoter polynucleotide in the viral genome that preferentially promotes transcription in cells expressing TERT contains no more than 82 consecutive nucleotides. The breadth of claim 38 is such that it reads on any consecutive 82 nucleotides of any promoter polynucleotide, wherein the promoter polynucleotide preferentially promotes transcription of said genetic element in cells expressing TERT. It is noted that neither claim 27 nor claim 38 contains any recitation limiting the promoter polynucleotide to sequences from the hTERT promoter (i.e. SEQ ID NO:1). Claim 40 is drawn to a method for producing said recombinant virus.

The instant issue is whether the specification provides enabling support commesurate in scope with the breadth of claims 27 and 38. The specification discloses only hTERT promoter polynucleotides and not any other promoter polynucleotides that would direct expression of a genetic element in cells expressing TERT. The specification discloses that pGRN175 (containing the hTERT promoter from position –117 to position –36; 82 consecutive nucleotides) directs expression of an operably linked reporter gene in immortal (HEK 293), but not mortal (BJ fibroblasts, RPE and HUVEC), cells (page 32, lines 5-7; page 34, lines 22-24 and lines 33-34). The specification discloses that pGRN266 (containing the hTERT promoter from position -2482 to position -36; 2446 consecutive nucleotides), pGRN267 (containing the hTERT promoter from position -239 to position -36; 203 consecutive nucleotides) and pGRN268 (***containing approximately 90 bp of hTERT promoter sequence and similar to pGRN175***), directed tumor cell line-specific expression of an operably linked thymidine kinase gene (page 35, lines 12-16). It is noted that the specification does not disclose the exact identity of pGRN268 (i.e. it is unclear which nucleotides of the hTERT promoter are contained within pGRN268). Thus, the specification discloses only hTERT promoter fragments that direct immortal cell line- and tumor cell line-specific gene expression; and of these hTERT promoter fragments the smallest clearly defined fragment that was examined contained the sequence from position –117 to position –36 of the hTERT promoter, the hTERT promoter being disclosed as SEQ ID NO:1. The specification does not disclose any other promoter polynucleotide containing no more

than 82 consecutive nucleotides that directs immortal cell line- and tumor cell line-specific gene expression.

The art of record at the time of the invention teaches the hTERT promoter. For example, Takakura **(Cancer Research, 59:551-557, 1999, IDS)** teaches isolation of the hTERT promoter and defines the polynucleotide regions of said hTERT promoter that are required for cancer cell line-specific expression of TERT. Specifically, Takakura teaches that a 1.4 kb 5' proximal region of the hTERT promoter directs TERT-positive cancer cell line-specific expression of an operably linked reporter gene (page 552, col. 2, paragr. 3, lines 9-12; page 555, Fig. 4A). Further, Takakura teaches that successive 5' deletions of said 1.4 kb 5' proximal region retain the ability of the promoter deletions to direct TERT-positive cancer cell line-specific expression of an operably linked reporter gene (page 553, col. 2, paragr. 1; page 554, Fig. 3; page 555, Fig. 4A). Takakura teaches that a construct termed pGL3-31 (containing the hTERT promoter from position –89 to position +1 according to the nomenclature of the instant specification; 88 consecutive nucleotides of the hTERT promoter), but not a construct termed pGL3 +19 (containing the hTERT promoter from position -58 to position +1, also according to the nomenclature of the instant specification; 59 consecutive nucleotides of the hTERT promoter) directed TERT-positive cancer cell line-specific expression of an operably linked reporter gene (page 553, col. 2, paragr. 1; page 554, Fig. 3; page 555, Fig. 4A). Takakura teaches that specific transcription factors (for example, c-Myc and Sp1) bind to specific regions of the hTERT promoter and that such transcription factors are likely responsible for the cancer-specific expression of TERT (page 554, col. 1,

paragr. 1, line 1 to col. 2, paragr. 1, line 12). Thus, the art of record at the time of the invention teaches a promoter polynucleotide containing the hTERT promoter from position –89 to position +1 that directs cancer cell line-specific gene expression. The art of record at the time of the invention teaches that hTERT promoter elements that direct cancer cell line-specific gene expression must be empirically mapped by trial and error.

In summary, an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate in scope with the instant claims. Such experimentation will be undue because of the unpredictability of directing cancer- or tumor-specific expression of a genetic element by operably linking said genetic element to any promoter polynucleotide consisting of any consecutive 82 nucleotides of said promoter polynucleotide; and because of the unpredictability of directing cancer- or tumor-specific expression of a genetic element by operably linking said genetic element to an hTERT promoter polynucleotide consisting of any consecutive 82 nucleotides. Neither the specification nor the art of record at the time of the invention provides sufficient guidance to address these issues for an artisan to practice the claimed invention.

Thus, limiting the scope of the claims to:

A recombinant virus having a genome in which a promoter polynucleotide is operably linked to a genetic element essential for replication or assembly of the virus, wherein the promoter polynucleotide consists of no more than 82 consecutive nucleotides consisting of the sequence from position –117 to position –36 relative to the translation initiation site (position 13545) of SEQ ID NO:1, and wherein the promoter

polynucleotide preferentially promotes transcription of the genetic element in cells expressing telomerase reverse transcriptase (TERT), thereby promoting replication of the virus, and wherein replication of the virus in a cell leads to lysis of the cell; and a method for producing said recombinant virus, is proper.

Written Description

Claims 27, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompasses a recombinant virus having a genome in which a promoter polynucleotide is operably linked to a genetic element essential for replication or assembly of the virus, wherein the promoter polynucleotide contains no more than 82 consecutive nucleotides and preferentially promotes transcription of the genetic element in cells expressing TERT, thereby promoting replication of the virus, and wherein replication of the virus in a cell leads to lysis of the cell; and a method of making said recombinant virus.

When claims 27, 38 and 40 are analyzed in light of the specification, the instant invention encompasses a recombinant virus having a genome in which any promoter polynucleotide containing any consecutive 82 nucleotides is operably linked to a genetic element essential for replication or assembly of the virus. Said promoter polynucleotide

is limited only to those promoter polynucleotides that preferentially promote transcription in cells expressing TERT and to those promoter polynucleotides that contain no more than 82 consecutive nucleotides. Such would encompass a large number of variants and molecules. However, the specification discloses only one species of said large number of variants and molecules: specifically, the sequence from position –117 to position –36 of the hTERT promoter (i.e. pGRN175) that promotes transcription of an operably linked reporter gene in immortal HEK 293 cells (page 32, lines 5-7; page 34, lines 22-24 and lines 33-34).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only one of the claimed species is disclosed (i.e. pGRN175).

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only identifying characteristic is that the promoter polynucleotide preferentially promote transcription in cells expressing TERT and that the promoter polynucleotide contain no more than 82 consecutive nucleotides of said promoter polynucleotide. Such a functional limitation cannot be an identifying characteristic for the claimed diverse genus of molecules because all of said molecules will have that characteristic.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Further, Applicant's attention is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In conclusion, Applicant's disclosure of one species of the of the claimed genus is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 recites, "The recombinant virus of claim 27, wherein the promoter polynucleotide comprises ***a binding site for a transcriptional regulatory element***." (emphasis added). Typically, such a binding site is itself a transcriptional regulatory element and transcription factors bind to the binding site and/or the transcriptional regulatory element. Thus, the recitation of claim 35 is indefinite.

It is noted that Examiner interprets claim 35 to read, --The recombinant virus of claim 27, wherein the promoter polynucleotide comprises a binding site for a transcription factor--.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 27, 29, 31, 32, 35, 40 rejected under 35 U.S.C. 102(e) as being anticipated by Martuza et al **(U.S. Patent 5,728,379, IDS)** as evidenced by Kim et al **(Science, 266:2011-2015, 1994)** and Kanazawa et al **(Biochemical and Biophysical Research Communications, 225:570-576, 1996)**.

Martuza teaches oncolytic replication-conditional recombinant virion that can be used as therapeutic vectors to treat cancer. Martuza teaches that a variety of tumor/cancer specific promoter polynucleotides (for example, see Tables 1 and 2) can be operably linked to a genetic element essential for the life cycle of said recombinant virion, wherein the promoter polynucleotide promotes transcription of said genetic element specifically in tumor or cancer cells, thereby promoting the lytic life cycle of the recombinant virion, thereby promoting death of the tumor or cancer cells.

Specifically, Martuza teaches a replication-conditional recombinant herpes virus having a genome comprising an albumin promoter, wherein said albumin promoter is operably linked to a genetic element encoding the herpes virus ICP4 protein, wherein the albumin promoter preferentially promotes transcription of the genetic element encoding the herpes virus ICP4 protein in an HuH7 hepatoma cell, thereby promoting conditional replication of said herpes virus and wherein conditional replication of said herpes virus in an HuH7 hepatoma cell leads to lysis of the cell (col. 19: lines 22-24, lines 39-41; claims 1, 2, 12 and 13). Martuza teaches said herpes virus further comprising the thymidine kinase suicide gene as an additional anti-tumor component when combined with the prodrug ganciclovir (col. 2, lines 1-4). Martuza also teaches a method for producing said replication-conditional recombinant adenovirus from a HepG2 hepatoma cell (col. 18, lines 26-36; claims 5-7).

It is noted that the instantly rejected claims contain no recitation requiring that the claimed recombinant virion comprise any element of a TERT promoter polynucleotide. Claim 27 merely recites, "wherein the promoter polynucleotide preferentially promotes

transcription of the genetic element in cells expressing telomerase reverse transcriptase (TERT)". The art of record at the time of the invention teaches that TERT is expressed in many immortal and cancer cells as evidenced by TERT activity. For example, Kim teaches that 90 of 101 biopsies representing 12 human tumor types, but none of 50 normal somatic tissues, were postitive for TERT activity (see Abstract of Kim et al). Further, Kanazawa teaches that human hepatocellular carcinoma derived cell lines, including HuH7 and HepG2 cells, exhibit TERT activity (page 574, lines 7-8). Thus, the teachings of Martuza are relevant, particularly when considering that Martuza used the HuH7 and HepG2 cell lines, because HuH7 and HepG2 cells inherently express TERT as evidenced by Kim and Kanazawa. Thus, the instant claims are anticipated by Martuza.

Claims 27-32, 35 and 40 are rejected under 35 U.S.C. 102(e) as being anticipated by Hallenbeck et al **(U.S. Patent 5,998,205, IDS)** as evidenced by Kim et al **(Science, 266:2011-2015, 1994)** and Kanazawa et al **(Biochemical and Biophysical Research Communications, 225:570-576, 1996)**.

Hallenbeck teaches oncolytic replication-conditional recombinant virion that can be used as therapeutic vectors to treat cancer. Hallenbeck teaches that a variety of tumor/cancer specific promoter polynucleotides (col. 6, lines 8-22) can be operably linked to a genetic element essential for the life cycle of said recombinant virion, wherein the promoter polynucleotide promotes transcription of said genetic element

specifically in tumor or cancer cells, thereby promoting the lytic life cycle of the recombinant virion, thereby promoting death of the tumor or cancer cells.

Specifically, Hallenbeck teaches a replication-conditional recombinant adenovirus having a genome comprising an α-fetoprotein (AFP) promoter, wherein said AFP promoter is operably linked to a genetic element encoding the adenovirus E1a protein, wherein the AFP promoter preferentially promotes transcription of the genetic element encoding the adenovirus E1a protein in an HuH7 hepatoma cell, thereby promoting conditional replication of said adenovirus and wherein conditional replication of said adenovirus in an HuH7 hepatoma cell leads to lysis of the cell (see col. 19 to col. 21, Example 1, particularly col. 19, lines 44-54; col. 21, lines 4-15; claims 1-4). Hallenbeck teaches a replication-conditional recombinant herpes virus analogous to said replication-conditional recombinant adenovirus (col. 10, lines 38-58). Hallenbeck teaches the recombinant viruses further comprising the thymidine kinase suicide gene as an additional anti-tumor component when combined with the prodrug ganciclovir (col. 13, lines 50-56; col. 22, line 66 to col. 23, line 4). Hallenbeck also teaches a method for producing said replication-conditional recombinant adenovirus from a HuH7 hepatoma cell (col. 17, lines 36-67; claims 11 and 18).

It is noted that the instantly rejected claims contain no recitation requiring that the claimed recombinant virion comprise any element of a TERT promoter polynucleotide. Claim 27 merely recites, "wherein the promoter polynucleotide preferentially promotes transcription of the genetic element in cells expressing telomerase reverse transcriptase (TERT)". The art of record at the time of the invention teaches that TERT is expressed

in many immortal and cancer cells as evidenced by TERT activity. For example, Kim teaches that 90 of 101 biopsies representing 12 human tumor types, but none of 50 normal somatic tissues, were postitive for TERT activity (see Abstract of Kim et al). Further, Kanazawa teaches that human hepatocellular carcinoma derived cell lines, including HuH7 cells, exhibit TERT activity (page 574, lines 7-8). Thus, the teachings of Hallenbeck are relevant, particularly when considering that Hallenbeck used the HuH7 cell line, because HuH7 cells inherently express TERT as evidenced by Kim and Kanazawa. Thus, the instant claims are anticipated by Hallenbeck.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hallenback et al **(U.S. Patent 5,998,205, IDS)** and Martuza et al **(U.S. Patent 5,728,379, IDS)** as evidenced by Kim et al **(Science, 266:2011-2015, 1994)** and Kanazawa et al **(Biochemical and Biophysical Research Communications, 225:570-576, 1996)** in view of Takakura et al **(Cancer Research, 59:551-557, 1999, IDS)**.

Both Hallenbeck and Martuza teach oncolytic replication-conditional recombinant virions that can be used as therapeutic vectors to treat cancer as put forth herein above under the 35 U.S.C. 102(e) rejections. Both Kim and Kanazawa teach that TERT is preferentially expressed in cancer cell lines, cancer biopsies and tumors when compared to normal cell lines and tissues where TERT is not expressed as put forth herein above under the 35 U.S.C. 102(e) rejections. Neither Hallenbeck nor Martuza specifically teach said virions comprising the hTERT promoter polynucleotide.

Takakura teaches isolation of the hTERT promoter and defines the polynucleotide regions of said hTERT promoter that are required for cancer cell line-specific expression of TERT. Specifically, Takakura teaches that a 1.4 kb 5' proximal region of the hTERT promoter directs TERT-positive cancer cell line-specific expression of an operably linked reporter gene (page 552, col. 2, paragr. 3, lines 9-12; page 555, Fig. 4A). Further, Takakura teaches that successive 5' deletions of said 1.4 kb 5' proximal region retain the ability of the promoter deletions to direct TERT-positive cancer cell line-specific expression of an operably linked reporter gene (page 553, col.

2, paragr. 1; page 554, Fig. 3; page 555, Fig. 4A). Lastly, Takakura, like Kim and Kanazawa, teach a strong correlation between TERT expression and telomerase activity in a variety of tumors and cancers (page 551, col. 2, lines 20-23).

It is noted that the 5' proximal regions of the hTERT promoter taught by Takakura to direct cancer cell-specific expression encompass the regions of the hTERT promoter claimed in the instant invention. For example, claim 36 recites the following nucleotide positions of SEQ ID NO:1 relative to the translation initiation site (i.e. position 13545 of SEQ ID NO:1): -239, -117, -36 and +1. Takakura uses a nucleotide numbering system based upon the transcription initiation site with the first nucleotide of the TERT mRNA being +1. Thus, -239 of the instant application equates with –181 of Takakura; -117 of the instant application equates with –59 of Takakura; -76 of the instant application equates with +1 of Takakura; -36 of the instant application equates with +41 of Takakura; and +1 of the instant application equates with +78 of Takakura. As such Takakura teaches hTERT promoter regions comprising the sequence from position –239 to position +1, said positions using the nucleotide numbering system of the instant application (i.e. the reporter construct taught by Takakara termed pGL3-181).

Further claim 37 recites that the promoter polynucleotide comprises at least about 100 or 500 consecutive nucleotides in SEQ ID NO:1. The reporter construct taught by Takakara termed pGL3-1375, for example, meets the limitations of claim 37.

Takakara does not specifically teach incorporation of hTERT promoter polynucleotide sequences into oncolytic replication-conditional recombinant virions.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the oncolytic replication-conditional recombinant virions taught by Hallenbeck and Martuza by substituting the regions of the hTERT promoter polynucleotide taught by Takakara with a reasonable expectation of success. Hallenbeck and Martuza teach that many cancer-specific promoters can be incorporated into said virions to direct cancer-specific replication and lysis of cancer cells which are infected by said virions. An artisan of ordinary skill would have been motivated to substitute the hTERT promoter polynucleotide because Kim, Kanazawa and Takakura teach that TERT is expressed in a cancer-specific manner and Takakura teaches the specific regions of the hTERT promoter that are capable of driving cancer-specific gene expression.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 27-37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hallenback et al **(U.S. Patent 5,998,205, IDS)** and Martuza et al **(U.S. Patent 5,728,379, IDS)** in view of Morin and Andrews **(U.S. Patent 6,610,839)**.

The applied reference (Morin and Andrews) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed

subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Both Hallenbeck and Martuza teach oncolytic replication-conditional recombinant virions that can be used as therapeutic vectors to treat cancer as put forth herein above under the 35 U.S.C. 102(e) rejections. Neither Hallenbeck nor Martuza specifically teach said virions comprising the hTERT promoter polynucleotide.

Morin teaches that the telomerase gene promoter directs expression of telomerase in immortal cell lines and a wide variety of tumors but not in normal somatic cells or in normal tissue adjacent to tumors (col. 2, paragr. 1). Morin teaches the hTERT promoter (SEQ ID NO:6), teaches that the sequence from position –2482 to position –36 of the hTERT promoter (2446 consecutive nucleotides of said promoter contained within a nucleic acid construct termed pGRN150) directs expression of an operably linked reporter gene in immortal cells (293 cells) but not in mortal cells (BJ cells) and concludes that this region of the hTERT promoter directs expression of operably linked genes in tumor cells but not in mortal cells (col. 180, paragr. 3).

Morin does not specifically teach incorporation of hTERT promoter polynucleotide sequences into oncolytic replication-conditional recombinant virions.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the oncolytic replication-conditional recombinant virions taught by Hallenbeck and Martuza by substituting the regions of the hTERT promoter polynucleotide taught by Morin with a reasonable expectation of success. Hallenbeck and Martuza teach that many cancer-specific promoters can be incorporated into said virions to direct cancer-specific replication and lysis of cancer cells which are infected by said virions. An artisan of ordinary skill would have been motivated to substitute the hTERT promoter polynucleotide because Morin teaches that TERT is expressed in a cancer-specific manner and that specific regions of the hTERT promoter are capable of driving cancer-specific gene expression.

Thus, the claimed invention as a whole was *prima facie* obvious.

Conclusions

No claims are allowed.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment and provide any statements that might help to identify support for the claimed invention (e.g. if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Dowell whose telephone number is 571-272-5540. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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